Biological Psychiatry

Commentary

Is Schizophrenia a Disorder of Accelerated Whole-System Aging?

Peter V. Kochunov and L. Elliot Hong

The term "accelerated aging" reflects the higher rates of aging-related clinical, biological, and functional decline observed in patients with many chronic conditions, including schizophrenia (1,2). In schizophrenia, this term echoes the historical narrative of Kraepelin's original definition of the disease as dementia praecox. This definition was based in part on the observations that the behavioral, cognitive, and postmortem brain findings in patients with schizophrenia resemble those in patients with senile dementia (3). Contemporary science has dismissed this definition because patients with schizophrenia do not show the irreversible cognitive decline implied by the term "dementia" (4). Instead, the term "accelerated aging" is used to emphasize that the age-related brain changes associated with schizophrenia appear abnormally faster than in control individuals. If patients with schizophrenia experience accelerated aging, the question becomes whether this trend is unique to the brain or is a part of general, accelerated whole-body aging. Furthermore, schizophrenia has traditionally been considered a mental illness characterized by psychosis, negative symptoms, and cognitive deficits. If accelerated aging occurs beyond the brain, it raises the question whether accelerated body aging is part of the schizophrenia syndrome or is caused by clinical processes linked to the disease, including higher rates of smoking, or to the metabolic effects of antipsychotic medications. In the current issue of *Biological Psychiatry*, Caspi *et al.* (5) provide an important perspective to understand the nonbrain aspects of the accelerated aging phenomenon in schizophrenia.

To date, most of the research on accelerated aging in schizophrenia has been focused on the brain. Caspi *et al.* (5) used genome-wide epigenetic methylation data derived from peripheral blood DNA to calculate and compare the difference between biological and chronological ages in participants with psychosis and control individuals. DNA methylation is a fundamental mechanism of transcriptional regulation; its changes across an individual's lifespan reflect not only genetics but also cumulative and present levels of stress, cellular senescence, telomere shortening, history of illness, exposure to toxins including tobacco and alcohol, and other biological mechanisms associated with health, aging, and disease. The overall functional roles and variations of methylation in transcriptional regulation across body organs, tissues, and cellular lines are still poorly understood. The methylation analyses were based on DNA extracted from diverse cellular lines present in whole blood, including monocytes, B cells, and T cells. The relative proportion of these cell types varies with age across populations and individuals. Further, each cellular line has unique aging-associated methylation profiles. Caspi *et al.* argued that this makes the choice of the biological clock algorithm an important consideration, as different methylation clock algorithms are trained to emphasize specific aspects of aging. Using 5 independent case-control samples and 5 algorithms, they calculated biological age from DNA methylation data and found that the DunedinPACE algorithm, developed by the authors, showed the highest elevation in biological age in patients with psychosis compared with control individuals (effect size = 0.22). This suggests that patients with psychosis aged at a rate ∼8% higher than control individuals, or an average difference between biological and chronological age of ∼3.2 years.

The finding of significantly higher biological age using DNA methylation from peripheral blood may be interpreted as evidence that accelerated aging in participants with psychosis involves a peripheral process beyond the brain. Indeed, people with schizophrenia have higher premature mortality rates and shorter than average lifespans—by as many as 20 years. The higher mortality rate in patients is explained by common illnesses in which advanced age is the chief risk factor, such as myocardial infarction, cerebrovascular events, cancers, and type 2 diabetes (1). Epidemiological surveys report that even young adult–to-middle-aged people with schizophrenia have a 1.5 to 3 times higher rate of chronic metabolic and cardiovascular illnesses for whom the older age is the main risk factor (6), and nearly 60% of young adults with psychosis meet the criteria for metabolic syndrome (7). Detecting, quantifying, and understanding the causes of a higher frequency of aging-related illnesses in patients with psychosis remains an unresolved challenge.

While there are no widely accepted biological measures of accelerated aging, Caspi *et al.* (5) provide a useful guide for developing more robust and reliable methodologies. Accelerated aging in schizophrenia and several other severe mental illnesses can be quantified across brain and body using linear and predictive modeling of normative aging trajectories. The individual deviations are interpreted in the context of the normative trajectories, and an individual's place on this trajectory provides the estimate of the biological age. Our group observed that people with schizophrenia show nearly twice the linear rates of aging-related decline in cerebral white matter integrity than control individuals (8). The regional pattern of accelerated aging mostly affected the frontal, temporal, and limbic white matter bundles that are critical for higher cognitive function, with a similar pattern of deficits observed in people with Alzheimer's disease versus mild cognitive impairment (9). We interpreted the finding as evidence for accelerated, neurodegenerative aging that particularly affected the

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structures that serve higher cognitive function in the brains of patients with schizophrenia (10). Tian *et al.* (2) applied predictive modeling across multiple body systems, including renal, cardiovascular, brain, and others, to rank the impact of chronic illnesses on an individual's biological age, and they found that schizophrenia was associated with the largest accelerated aging effects among metabolic, neurological, and mental disorders. In fact, patients with schizophrenia showed higher differences between biological and chronological age (~2.8 years) than any other neurodegenerative aging condition, including dementia and Parkinson's disease (2). The findings by Tian *et al.* and now Caspi *et al.* suggest that accelerated aging in schizophrenia occurs not just in the brain but also in the body. Whether they are parallel processes or have a cause–consequence relationship is less clear, as fully answering this question may require both brain and periphery measures.

Accelerated aging in schizophrenia can be a part of the general pathology of this illness or caused by external factors, including substance and medication use. Caspi *et al.* (5) quantified accelerated aging using 5 independent algorithms that were designed to tease out specific aspects and causes of aging. For example, patients with mental illness have higher rates of tobacco, alcohol, and other substance use, and this may contribute to accelerated aging because these substances have known negative impacts on the body and the brain. The GrimAge algorithm was 1 of 5 algorithms they used to calculate biological age in the cohorts of people with psychosis. The GrimAge algorithm was specifically trained using the methylation profiles of tobacco smoking and other substance use; however, this algorithm reported no significant difference in aging trends between cases and control individuals. The effect size of the gap between biological and chronological ages (effect size = 0.02) for cases was the smallest of all algorithms. Caspi *et al.* argued that this answered the question on whether tobacco smoking or other substance use is the culprit for accelerated aging in schizophrenia.

Another important consideration is whether medications taken by patients with psychosis may directly or indirectly contribute to accelerated brain and body aging. As antipsychotic medications increase the risks for metabolic syndrome and other side effects, this is likely, although the cumulative antipsychotic and antidepressant dose did not significantly contribute or explain the aging-related individual variances in brain measurements (10). Likewise, all 5 methylation clock algorithms showed no significant differences between patients who were prescribed clozapine when compared with those who used other antipsychotic medications. The authors interpreted this finding as showing that psychosis severity was not associated with aging pace. Our reservation with this conclusion stems from an incomplete understanding of how clozapine impacts methylation profiles of blood cell lines. Clozapine is often prescribed in the most severe cases of psychosis in patients who are refractory to standard antipsychotic regimens. As one of the most effective antipsychotic medications, clozapine may also have reduced accelerated aging caused by schizophrenia-related pathology. In conclusion, Caspi *et al.* (5) have meaningfully advanced the knowledge of and methods used to understand the peripheral epigenetic aging process in schizophrenia. They provide new approaches to test whether these peripheral effects are relevant to accelerated brain aging, highly elevated aging-related medical morbidity and mortality, and potentially even an accelerated whole-system aging process in this patient population.

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Article Information

From the Faillace Department of Psychiatry and Behavioral Sciences at McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, Texas.

Address correspondence to Peter V. Kochunov, Ph.D., at peter.kochunov@uth.tmc.edu.

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